

We claim:

1. A method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell, comprising:

5 (a) culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject;

(b) transfecting said epidermal basal cell, in vitro, with one or more eukaryotic expression vector(s) containing at least one cDNA encoding a human neurogenic transcription factor, or homologous non-human counterpart, or active fragment(s) thereof, from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, such that at least one of the neurogenic transcription factor(s) is expressed in said cell;

10 (c) growing the transfected cell in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or human HES1 gene, or homologous non-human counterpart of either of these, thereby suppressing at least one negative regulator of neuronal differentiation; and, optionally,

15 (d) growing said epidermal cell with a retinoid and at least one neurotrophin selected from the group consisting of BDNF, CNTF, PDGF, NGF, NT-3, NT-4, sonic hedgehog, and active fragments of any of these, or a cytokine comprising IL-6, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell.

20 2. The method of Claim 1, wherein the eukaryotic expression vector(s) of the transfection step comprise a CMV promoter sequence operatively linked to a DNA(s) encoding the neurogenic transcription factor selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, and wherein the DNA encoding the neurogenic transcription factor is of human origin or is a homologous non-human counterpart, or is an active fragment of a gene encoding any of these.

25 3. The method of Claim 1, wherein the physiological and/or immunological feature is expression of a marker selected from the group consisting of nestin, neural RNA-binding protein Musashi, neurofilament M, neural-specific β -tubulin, neural-specific enolase, microtubule associated protein 2, glial fibrillary acidic protein (GFAP), O4, or a combination of any of these.

30 4. The method of Claim 1, wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length.

5. A transdifferentiated cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell, comprising:

an epidermal basal cell transfected with one or more expression vectors comprising a CMV promoter sequence operatively linked to a DNA(s) encoding the neurogenic transcription factor NeuroD1, NeuroD2, ASH1, Zic1, Zic3, or MyT1, wherein the DNA encoding the neurogenic transcription factor is of human origin, or is a non-human homologous counterpart, or is an active fragment of a gene encoding any of these, said cell being treated with at least one antisense oligonucleotide comprising a segment(s) of human MSX1 gene or human HES1 gene, or non-human homologous counterpart thereof, and wherein said cell was grown in the presence of a retinoid and at least one neurotrophin, thereby transdifferentiating said epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell.

6. The transdifferentiated cell of Claim 5, wherein the physiological and/or immunological feature is expression of a marker selected from the group consisting of nestin, neural RNA-binding protein Musashi, neurofilament M, neural-specific β -tubulin, neural-specific enolase, microtubule associated protein 2, glial fibrillary acidic protein (GFAP), O4, or a combination of any of these.

7. The transdifferentiated cell of Claim 5, wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length.

8. A transdifferentiated cell produced by the process of Claim 1.

9. The transdifferentiated cell of Claim 8, wherein the physiological and/or immunological feature expressed by the cell is a marker selected from the group consisting of nestin, neural RNA-binding protein Musashi, neurofilament M, neural-specific β -tubulin, neural-specific enolase, microtubule associated protein 2, glial fibrillary acidic protein (GFAP), O4, or a combination of any of these.

10. The transdifferentiated cell of Claim 8, wherein the morphological feature expressed by the cell is one or more morphological neurite-like process(es) at least about 50 micrometers in length.

11. A kit for converting epidermal basal cells to cells into cells having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell, said kit comprising:

(A) one or more eukaryotic expression vector(s) containing cDNA encoding a neurogenic transcription factor, or fragment thereof, from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, or a non-human homologous counterpart of any of these;

(B) at least one antisense oligonucleotide corresponding to the human MSX1 gene, the human HES1 gene, or a non-human homologous counterpart of either of these; and

(C) a retinoid and at least one neurotrophin from the group consisting of BDNF, CNTF, PDGF, NGF, NT-3, NT-4, and sonic hedgehog.

12. The kit of Claim 11, further comprising instructions for using (A), (B), and (C) in transdifferentiating a mammalian subject's epidermal basal cell(s).

5 13. A method of using transdifferentiated epidermal basal cells having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell to isolate a novel nerve growth factor, comprising:

10 (a) transdifferentiating epidermal basal cells to cells having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell as in Claim 1;

(b) culturing the transdifferentiated cells in vitro;

(c) exposing the cultured cells, in vitro, to a potential nerve growth factor; and

15 (d) detecting the presence or absence of an effect of the potential nerve growth factor on the survival of the cells or on a morphological or electrophysiological characteristic and/or molecular biological property of said cells, whereby an effect altering cell survival, an electrophysiological characteristic and/or a molecular biological property in the cells indicates the action of the novel nerve growth factor.

20 14. A method of using transdifferentiated epidermal basal cells having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell to screen a potential new drug for treating a nervous system disorder, comprising:

(a) transdifferentiating epidermal basal cells from a patient with a nervous system disorder to cells having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell as in Claim 1;

25 (b) culturing the transdifferentiated cells in vitro;

(c) exposing the cultured cells, in vitro, to a potential new drug; and

30 (d) detecting the presence or absence of an effect of the potential new drug on the survival of the cells or on a morphological or electrophysiological characteristic and/or molecular biological property of said cells, whereby an effect altering cell survival, an electrophysiological characteristic and/or a molecular biological property in the cells indicates the action of the potential new drug factor.

15. A transdifferentiated epidermal basal cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell, wherein

the physiological and/or immunological feature expressed by the cell is a marker selected from the group consisting of nestin, neural RNA-binding protein Musashi, neurofilament M, neural-specific β -tubulin, neural-specific enolase, microtubule associated protein 2, glial fibrillary acidic protein (GFAP), O4, or a combination of any of these.

5 16. The transdifferentiated cell of Claim 15, wherein the cell further displays the physiological feature of a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

17. The cell of Claim 15, wherein the transdifferentiated cell has a morphological, physiological, or immunological feature specific to a neuronal cell.

10 18. The transdifferentiated cell of Claim 17, wherein the physiological and/or immunological feature is expression of neural RNA-binding protein Musashi, neurofilament M, neural-specific β -tubulin, neural-specific enolase, microtubule associated protein 2.

19. The transdifferentiated cell of Claim 17, wherein the cell is a GABAergic cell.

20. The transdifferentiated cell of Claim 17, wherein the cell is a dopaminergic cell.

15 21. The transdifferentiated cell of Claim 15, wherein the morphological feature is one or more neurite-like process(es) at least about 50 micrometers in length.

22. The transdifferentiated cell of Claim 15, wherein the cell is of human origin.

23. The cell of Claim 15, wherein the transdifferentiated cell has a morphological, physiological, or immunological feature specific to an astroglial or oligodendroglial cell.

20 24. The transdifferentiated cell of Claim 23, wherein the physiological and/or immunological feature is expression of glial fibrillary acidic protein (GFAP) or O4.

25 25. A cell culture derived from the transdifferentiated cell of Claim 15, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell.

26. The method of Claim 1, wherein culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s) comprises separating basal cells from keratinocytes using a calcium-free medium.

27. The method of Claim 1, wherein said antisense oligonucleotide(s) is modified with one or more thio groups.

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